REMARKS

Claims 1-8 (not 1-7, as stated in the Detailed Action) were non-elected and have now been canceled, without prejudice. Claims 9-16 were examined in the last Action. Applicant has now canceled claims 9-16, without prejudice, and added new claims 17-37. Of the new claims, only claim 17 is independent.

Claim 17 recites a coding system of a mixture of signaling hairpin molecules that includes multiple affinity pairs and multiple fluorophores. Literal support for these limitations is found at page 5, lines 14 and 27, respectively. No issue of new matter is seen. Claim 18 derives from original claim 2. Claims 19 and 20 derive from original claim 4. Claim 21 is supported by the specification at page 13, lines 21-23, where decoding each bead in a mixture is described. Claim 22 derives from original claim 3. Claim 23 derives from original claim 11. Claim 24 derives from original claim 6. Claim 25 derives from original claim 16. Claim 26 is supported by the specification at page 5, lines 9-12. Claim 27 derives from original claim 10. Claim 28 is supported by the specification at page 8, lines 9-11. Claim 29 derives from original claim 13. Claim 30 derives from original claim 6. Claim 31 derives from original claim 10. Claim 32 derives from original claim 11. Claim 33 derives from original claim 12. Claim 34 derives from original claim 16. Claim 35 derives from original claim 13. Claim 36 derives from original claim 16. Claim 37 derives from original claim 8. No issue of new matter is seen for dependent claims 18-37.

Drawings

Fig. 3 is objected to as lacking SEQ ID Nos. The drawings referred to in the Office Action Summary are the original drawings filed 02 March 2004. However, the Examiner has apparently not taken notice that a corrected Fig. 3 was previously filed on August 9, 2004, and overcomes the noted objection. The Examiner is kindly requested to acknowledge in the next communication that the August 9, 2004 drawing is acceptable.

Specification

The specification is objected to at the Description of Drawings because of the objection to Fig. 3. The specification has been amended above and now overcomes the objection.

Claim Objections

Claim 9 is objected to as referring back to non-elected claims. Claims 9-16 are replaced above by new claims 17-34. Independent claim 17 replaces independent claim 9 and is seen to overcome the objection to claim 9 stated in paragraph 4 of the Action.

Claim Rejections – 35 USC § 103

Claims 9-13 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Bruchez, Jr. et al., U.S. Patent 6,500,622 ("Bruchez") in view of Bonnet et al. (1999) Proc. Nat. Acad. Sci. 96: 6171-6176 ("Bonnet"), the Examiner asserting (Action, page 9) that it would be *prima facie* obvious to combine the affinity pairs taught by Bonnet with the affinity pairs taught by Bruchez. Claims 13-16 are rejected under 35 U.S.C. 103(a) over the foregoing references further in view of Fan et al. U.S. Patent 6,890,741 ("Fan").

Turning first to Bruchez, the primary reference, one finds that it discloses encoded microcarriers having immobilized capture probes on their surfaces. Molecular beacon probes are specifically disclosed as capture probes. Molecular beacon probes are oligonucleotide hairpins having a stem, or affinity pair, in which one hybridized arm is labeled with a fluorophore and the other hybridized arm is labeled with a quencher such as dabcyl. One can tell if a particular microcarrier has picked up a target by determining whether or not the molecular beacon's fluorophore has been unquenched and is emitting. See Example 2, beginning in column 38, and Example 4, beginning in column 40, wherein either four different microcarriers or two different microcarriers each have a different molecular beacon capture probe capable of hybridizing to, and immobilizing to its microcarrier, a particular sequence. All molecular beacon capture probes in both examples were labeled with the fluorophore fluorescein and the quencher dabcyl.

Detected fluorescein emission from a particular microcarrier indicates that some analyte sequence has hybridized to that microcarrier and that the microcarrier must be decoded to learn which capture probe sequence was the one that hybridized. (An embodiment disclosed in columns 34-35 called a "Loop Probe Assay" utilizes unlabeled molecular-beacon-type hairpin capture probes and targets that are fluorophore-labeled by synthesizing them from a fluorophore-labeled primer (same primer for two possible alleles in a PCR amplification reaction) with the same result after unincorporated primers are washed away – namely, beads where targets hybridized to the capture probes signal that fact and must be decoded.) The assay of newly presented claim 17 also uses capture probes for the purpose of capturing analyte sequences, and the capture probes may be molecular beacon probes as specifically recited in newly presented dependent claim 37. It is not capture probes, but rather microcarrier coding, that distinguishes claim 17 from Bruchez and the other cited references.

Coding taught by Bruchez is the "dye" in the microsphere. See column 30, line 62:

> The invention described here is the attachment of MBs [molecular beacon capture probes] onto encoded microspheres dyed with one or more different kind of SCNCs [semiconductor nanocrystals].

See also column 17, lines 58-63, which refers to beads [microspheres] encoded with SCNCs, fluorophores, chromophores, or combinations thereof. See column 18, beginning at line 36: because SCNCs have very narrow emission spectra, of the order of 5-10 Angstroms, some 3000 codes can be obtained using for each bead one short wavelength SCNC (within the range 490-565 Angstroms) and one long wavelength SCNC (within the range 575-650 Angstroms). The emission characteristic of a particular SCNC depends on size, size distribution, and composition, and is set when the SCNC is made (column 25, line 28).

In an assay, the individual microspheres whose capture probes are fluorescent are investigated to determine their spectral code, that is, the SCNC or combination of SCNCs. This is the signature that identifies which molecular beacon capture probe has hybridized to its target.

The system of Bruchez is very different from the system of the claimed invention. Referring to independent claim 17, an individual microcarrier has immobilized on its surface two types of molecules: a capture probe, which in some embodiments will be, as noted above, a molecular beacon as in Bruchez; and hairpin molecules that carry the code. These hairpin molecules are not SCNCs, fluorophores or chromophores, which Bruchez discloses may be dyes added to the microspheres. The hairpin molecules of claim 17 comprise affinity pairs that are sensitive to temperature or some other environmental condition and that are labeled with quenched fluorophores. The coding scheme is to use combinations of multiple (see dependent claim 20, which recites three-to-eight) fluorophores and multiple affinity pairs (see dependent claim 19, which recites at least three). The signaling hairpins are decoded to determine which capture probes have successfully hybridized to an analyte sequence. For example, when a capture probe's hybridization is detected for a particular microcarrier, its hairpin molecules are interrogated to identify which capture probe sequence has hybridized. A particular microcarrier may show fluorescein and Texas red emission when the temperature is raised to a first level (opening and unquenching a first hairpin molecule), and also tetramethyl rhodamine emission when the temperature is raised to a second level higher than the first level (opening and unquenching a second hairpin molecule). The combination of color(s) and temperature(s) of the immobilized hairpin molecules comprises the code in this example. At temperatures below the first temperature, the signaling hairpins immobilized on the surface of the microcarrier are dark.

The Examiner has stated a number of conclusions regarding Bruchez at pages 6-9 of the Action. Applicant addresses only some of those conclusions here, it being understood that, in view of the distinguishing explanation set forth above, not addressing another point specifically does not signify agreement with the Examiner's conclusion. The Examiner cites Bruchez col. 7,

lines 40-52, with reference to the signaling "probes" of Applicant's claim 1 (now withdrawn). The cited passage in col. 7 of Bruchez in fact describes the use of unlabeled capture probes, in which case the targets are labeled to indicate when hybridization has occurred. In such a case, the use of a different fluorophore label can be added to each target when it is copied, as by PCR amplification. The fluorophore on a strand captured by a bead indicates that an analyte strand has been captured, and the intensity of analyte signal can be used for quantification. There is no disclosure of using the targets' labeling as a coding scheme of claim 17. It is the microspheres, not the capture probes, and certainly not the hairpin signaling molecules, that are encoded in Bruchez. The Examiner cites Bruchez col. 35, lines 9 et seq. as disclosing the use of multiple environmental conditions, including temperature and denaturant, for disruption of encoded hairpin stems. Col. 35 merely reports that molecular beacon or molecular beacon-type hairpin capture probes are very specific, and their desired operation to hybridize to one allele, but to ignore another allele, can be tailored by choosing proper assay design factors such as temperature and salt concentration; and that if the assay is properly designed, such capture probes are allele specific over a wide temperature range of 30-45 °C (see Bonnet for the thermodynamic explanation of why molecular beacon probes have a wide temperature window of allele discrimination). Col. 35 addresses the capture probes. It does not disclose the use of signaling hairpins, coding signaling hairpins, or changing a condition as part of decoding signaling hairpins. It does not even disclose changing conditions as part of detecting which capture probes have hybridized so as to determine which microspheres to decode.

At page 7 of the Action, the Examiner states that the fact that each molecular beacon will bind to a perfectly complementary allele at a much higher temperature than it will bind to another (mismatched) allele teaches that disruption occurs at different conditions. However, as noted above, this teaching relates to capture probes, not signaling molecules, and Bruchez teaches using a single condition at which disruption of signaling probes occurs only for perfectly matched targets. There is no suggestion of using different conditions as part of decoding signaling hairpins. There is no suggestion even of using different conditions as part of capture

with molecular beacon probes. The Examiner notes that at col. 24 Bruchez discloses a list of fluorophores. Bruchez does not disclose use of combinations of fluorophores on signaling hairpins as required for the coding scheme of claim 17.

Similarly, with regard to the use of a flow cytometer, Bruchez discloses such use to detect which capture probes have hybridized and to measure the intensity from that hybridization for quantitation. This is what is taught in Example 2, col. 39, which the Examiner cites. There is no disclosure in col. 39 of using a flow cytometer as part of decoding.

Not only does Bruchez not disclose the coding scheme of claim 17, Bruchez teaches away from the coding scheme of claim 17. It teaches that one may use hairpin molecules (molecular beacons or unlabeled probes) as capture probes, but it excludes hairpin molecules as the encoding scheme. This is seen as a clear teaching away.

Bonnet does not supply what Bruchez is missing. It discloses that molecular beacon probes have higher melting temperatures to perfectly complementary targets than to targets having one or more mismatched nucleotides. Bonnet explains the allele-discriminating power of molecular beacons that Bruchez utilizes in its very specific capture probes, including the capture probes for SNP detection in Example 4. There is no disclosure or suggestion in Bonnet to encode microcarriers with quenched hairpin molecules having different combinations of affinity pairs and quenched fluorophores. The Examiner cites Bonnet for its disclosure in Table 1 that mismatches alter the temperature at which a molecular beacon will open. The salient fact, however, is that Bonnet does not disclose or suggest hairpin signaling molecules, coding the same, or decoding the same using a change in environmental conditions. Bonnet does not teach or address coding. Bonnet adds nothing to Bruchez in this pertinent regard. Bonnet provides no motivation to substitute the coding scheme or decoding process of claim 17 for the coding scheme and decoding process of Bruchez.

Fan is not cited by the Examiner for disclosure of any coding scheme or for suggesting the coding scheme or decoding process of claim 17; that is, Fan is not alleged to cure the defects of Bruchez.

For at least the foregoing reasons, the rejections based on Bruchez are misplaced with respect to the now-pending claims. The claims would not have been obvious to one of ordinary skill in the art over the cited references at the time the invention was made.

Conclusion

In any event, for at least the reasons indicated above, all pending claims are allowable and the issuance of a notice of allowance is proper and is urged.

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

The fees in the amount of $535 for the required excess claim fee and three-month extension of time, are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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